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Chronic Pelvic Pain of Bladder Origin:

A Focus on Interstitial Cystitis

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Statement of Need

Interstitial cystitis is commonly misdiagnosed in women as overactive bladder, recurrent urinary tract infection, or endometriosis; in men it is often mistaken for prostatitis. The impact of interstitial cystitis on a patient's quality-of-life (QOL) is significant — these women score lower on QOL inventories than do dialysis patients; in men, the impact is comparable to that of patients with myocardial infarction, angina, or Crohn's disease. Therefore, effective diagnostic methods, understanding of epidemiology and demographics, and proper identification of nonpharmacologic and pharmacologic options are necessary for the management of interstitial cystitis.

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This monograph should take approximately 2 hours to complete. The participant should, in order, read the objectives and monograph, answer the 10-question multiple-choice post-test, placing answers on the Registration/Post-Test Answer Form/Evaluation on page 22. The evaluation form provides each participant with the opportunity to comment on the quality of the instructional process, the perception of enhanced professional effectiveness, the perception of commercial bias, and his or her views on future educational needs. To receive credit for this activity, follow the instructions provided on the post-test and evaluation form. This credit will be valid through August 31, 2005. No credit will be given after that date.

Educational Objectives

Upon completion of this program, participants will be able to:

- Differentiate between chronic pain of pelvic versus bladder origin
- Discuss the epidemiology and demographics of chronic pelvic pain and interstitial cystitis
- Discuss the theories underlying the pathophysiology of interstitial cystitis
- Discuss the impact of interstitial cystitis and chronic pelvic pain on quality of life
- Discuss the evolving roles of the Pelvic Pain Urgency and Frequency Patient Symptom Scale, Potassium Sensitivity Test, and other diagnostic tools in identifying patients with interstitial cystitis
- Identify nonpharmacologic and pharmacologic options for the management of interstitial cystitis

Target Audience

Obstetrician/gynecologists, urologists, family physicians, nurse practitioners, and physician assistants.

For additional continuing medical education opportunities related to this subject, visit the U.S. Department of Health and Human Services' Office on Women's Health Web site at: www.4woman.gov/healthpro/contedu.

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CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS

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INTRODUCTION

Abnormal uterine bleeding and chronic pelvic pain (CPP) are two common gynecologic symptoms. Gynecologists can usually diagnose and manage the various causes of abnormal uterine bleeding without difficulty by utilizing several validated diagnostic techniques/procedures and effective medical and surgical treatment modalities that are currently available. In contrast, the diagnosis and treatment of CPP is more challenging. CPP is commonly not associated with any histologic abnormality, and despite laparoscopic visualization of pelvic organs, an etiology for the CPP is frequently not determined. Among the many common causes of CPP are intraperitoneal pelvic causes, such as endometriosis, salpingitis, posthysterectomy, and intraperitoneal adhesions, and urogenital causes, including vulvodynia, urinary tract infection (UTI), and overactive bladder (OAB). An increasing number of women with CPP have been found to have an etiology of bladder origin — specifically, interstitial cystitis (IC).

CPP is a major public health concern, affecting approximately 15% of the adult female population in the United States.[1] The morbidity associated with CPP is also considerable: it is estimated that nearly 15% of referrals to gynecologists from general and family practitioners are done for CPP.[2] The chronicity and severity of the pain and urologic symptoms associated with chronic pelvic pain syndrome (CPPS) can profoundly impact a patient's quality of life (QOL) limiting her/his ability to work full-time or to participate in regular home and sexual activities. The economic ramifications of CPP are staggering, totaling an estimated $3.3 billion per year in the US.[1] The medical, psychological and financial benefits of prompt and accurate diagnosis and treatment of CPP cannot be underestimated.

Interstitial cystitis (IC) is a CPPS of bladder origin that is now known to be a common cause of CPP in both women and men. IC is manifested by symptoms of urinary urgency and frequency and/or pelvic discomfort or pain in the absence of other overt bladder pathology (such as UTI or bladder cancer). The clinical presentation of IC is similar to that of other CPPS; however, IC was (and continues to be) overlooked because gynecologists rarely consider the bladder to be an etiology of CPP, frequently leading to misdiagnoses of endometriosis, pelvic adhesions, or vulvodynia. Similarly, men with IC are frequently (mis)diagnosed with nonbacterial chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

Until recently, there were no highly effective diagnostic techniques or therapeutic regimens utilized specifically for CPP of bladder origin; in fact, there was great diversity in the management of IC, and the diagnostic assessments utilized primarily identified only those patients with severe disease. The introduction of two new diagnostic modalities — the Pelvic Pain Urgency/Frequency Patient Symptom Scale (PUF) and the Potassium Sensitivity Test (PST) — and the approval of the first oral therapeutic agent — pentosan polysulfate sodium (PPS) — will help clinicians readily identify and treat patients whose CPP is due to a bladder abnormality, facilitating appropriate therapy and an enhanced QOL.

CHRONIC PELVIC PAIN SYNDROMES IN WOMEN

In March 2004, the American College of Obstetricians and Gynecologists published a Practice Bulletin on Chronic Pelvic Pain which defined CPP as: "Non-cyclic pain of 6 or more months duration that localizes to the anatomic pelvis, abdominal wall at or below the umbilicus, lumbosacral back, or the buttocks and is of sufficient severity to cause functional disability or lead to medical care."[3] CPP in women is far more prevalent than previously believed, with an estimated prevalence of 3.8% in women, comparable to the prevalence of migraine (2.1%), asthma (3.7%), and back pain (4.1%) (Table 1).[4] CPPS affect at least one in seven (and possibly as many as one in three) women in the United States at some point during their lives.[2] The majority of the estimated 9 to 15 million women in the US affected by CPP are young, premenopausal women in whom the symptoms first occur.[1] CPP is an indication for nearly 18% of hysterectomies and 20% of laparoscopies performed in the US, although more than 60% of diagnostic laparoscopies for CPP reveal no evidence of pelvic pathology.[5-7] The cost of CPP in the US is considerable: estimates 10 years ago indicated direct medical costs of outpatient physician visits for CPP were $881.5 million annually, and out-of-pocket direct expenses were estimated to be $1.9 billion annually.[1] Indirect costs associated with lost work time totaled another $555.3 million annually, leading to total direct and indirect costs of CPP of approximately $3.3 billion annually.[1] It is apparent that CPPS is a major public health concern.

Table 1

CHRONIC PELVIC PAIN: MAGNITUDE OF THE PROBLEM

- Affects 9 to 15 million American women
  - ~15% of adult female population[1]
  - May affect 1 in 7 — and possibly 1 in 3 — women[2]
- Estimated prevalence of 3.8%[4]
  - Comparable to migraine, asthma, back pain
  - Chronic pelvic pain is indication for ~18% of hysterectomies[5] and 20% laparoscopies[5]
    - >60% diagnostic laparoscopies reveal no evidence pelvic pathology[6,7]
- Annual cost in US significant: ~$3.3 billion[1]

The clinical presentation of CPPS in women includes the presence of chronic pain in the lower abdomen, vulva, urethra, vagina, medial thighs, and/or perineum; frequent UTI or voiding symptoms of urinary urgency and/or frequency; dyspareunia; perimenstrual exacerbations, and

exacerbations after sexual intercourse (Table 2). There are many possible etiologies associated with this complex of symptoms, including intraperitoneal pelvic causes, urogenital causes, and CPP of bladder origin or IC. Often, the same patient can concurrently have multiple etiologies of CPP, such as endometriosis and IC. Failure to take a complete bladder history as part of the routine gynecologic work-up — which would quickly identify the CPP to be of bladder origin — contributes to an overemphasis on determining that problems with the intraperitoneal pelvic for the etiology causes CPP when the etiology is, actually, of bladder origin. Clinicians must therefore remember to also consider that a bladder abnormality is a possible etiology of CPP.

Table 2

CHRONIC PELVIC PAIN SYMPTOMS IN FEMALE PATIENTS

- Chronic pain in lower abdomen, vulva, urethra, vagina, medial thighs, perineum
- Recurrent symptoms consistent with urinary tract infection (frequency/urgency)
- Dyspareunia
- Perimenstrual exacerbations
- Exacerbations after sexual intercourse

Intraperitoneal Pelvic Causes of Chronic Pelvic Pain

The most common etiologic diagnoses for the cause of CPP are intraperitoneal pelvic conditions such as endometriosis, pelvic infection, post-hysterectomy abnormalities, and other intraperitoneal pelvic adhesions (Table 3). Adenomyosis, gastrointestinal disorders, and pelvic floor dysfunction are also etiologies of CPP. Endometriosis is the most common identifiable cause of CPP, affecting 70% to 90% of women with CPP.[5] However, recent data indicate that one in three women with endometriosis also have concurrent IC, leading some clinicians to consider endometriosis and IC "evil twins".[8,9] In a recent retrospective study, 60 women with CPPS underwent concurrent laparoscopy and cystoscopy and hydrodistention.[9] Fifty-eight of the sixty women were diagnosed as having IC (based upon bladder wall glomerulations visualized with cystoscopy), and 56 were diagnosed as having endometriosis (80% of whom had biopsy-proven endometriosis). Fifty-four of the 56 women diagnosed with endometriosis had concurrent IC, and 54 of the 58 women diagnosed with IC had concurrent endometriosis.[9] This study emphasizes the need for clinicians to always consider the bladder to be a source of CPP among patients who present with symptoms suggestive of endometriosis.

Table 3

INTRAPERITONEAL PELVIC CAUSES OF CHRONIC PELVIC PAIN

- Endometriosis
- Pelvic infection
- Post-hysterectomy abnormalities
- Intraperitoneal adhesions

Salpingitis and other causes of pelvic inflammatory disease (PID) can also present with symptoms of CPP. CPP can develop after one or more episodes of PID; in fact, a causal relationship has been established between untreated chlamydial infection, PID, and CPP.[10] In addition, post-surgical intra-abdominal adhesions have been identified as a common cause of CPP.[11-13] Intra-abdominal pelvic adhesions currently account for approximately 3% of all surgical admissions to hospitals in the Western world, and the presence of adhesions is strongly associated with, and predictive of, pelvic pain severity.[12,14]

CPP is an indication for an estimated 18% of hysterectomies performed in the United States.[5] However, more than 1 in 4 women continue to experience persistent pelvic pain after hysterectomy, and 4% to 9% of women continue to have urinary problems.[15-19] Often, women who undergo a hysterectomy solely to resolve CPP will experience a recurrence of the pain within 6 to 12 months which is usually believed to be due to adhesions, when, in fact, the patient has IC. This finding was recently demonstrated in a study in which 79% of women who have had a hysterectomy and presented to a CPP clinic with persistent pain had a positive potassium sensitivity test – a finding highly suggestive of a bladder cause of the CPP.[9] These data indicate that IC should always be considered as a possible source of CPP in women before they undergo hysterectomy for persistent pelvic pain.

Urogenital Causes of Chronic Pelvic Pain

Urogenital syndromes are another common cause of CPP in women. As with intraperitoneal pelvic causes, women with urogenital syndromes present with pelvic pain and voiding symptoms that include urinary urgency and frequency. Among the most common urogenital causes of CPP are vulvodynia, overactive bladder (OAB), recurrent UTI, and IC (Table 4).

Vulvodynia

Vulvodynia is a multifactorial syndrome that includes five different conditions, of which only one — vulvar vestibulitis syndrome (VVS) – appears to be related to CPP of bladder origin.[20] Vulvodynia is almost exclusively diagnosed in Caucasian women and persists as an acute onset of vulvar pain, soreness, rawness, burning, or stinging. Without effective treatment, the pain becomes chronic. It is estimated that 15% of women in a general gynecology practice are affected by one of the five subclassifications of vulvodynia.[20]

Table 4

UROGENITAL CAUSES OF CHRONIC PELVIC PAIN

- Vulvodynia
- Urinary tract infection
- Overactive Bladder
- Interstitial Cystitis

Women with VVS have chronic and severe tenderness or pain with intercourse or vestibular touch and introital erythema.[21] VVS primarily affects younger women and is thought to be one of the most common causes of dyspareunia among premenopausal women.[22] Acute VVS typically has a specific etiology, such as human papillomavirus (HPV), an allergic event, or an autoimmune process; however, similar symptomatology for both chronic VVS and IC can confuse the diagnosis.

Vulvar dermatoses are painful infections or diseases of the vulvar skin, such as herpes, fungal infections, lichen sclerosis, lichen planus, or thinning of the introital tissue as a result of estrogen deprivation. Vulvar dermatitis is the cause of approximately 50% of the vulvar dermatoses and presents as thick or scaly vulvar lesions, erythema, and itching.[23,24] *Vulvovaginitis,* or *cyclic candidiasis,* is another common cause of vulvodynia. Cytolytic vaginosis (CV) infection presents similarly to cyclic candidiasis albeit with a luteal-phase pattern of symptom recurrence.[25] *Vestibular papillomatosis* is either caused by HPV or by a normal anatomic variation and requires a biopsy for diagnosis. *Dysesthetic (or essential) vulvodynia* occurs in perimenopausal or postmenopausal women who experience diffuse and constant vulvar pain or burning without tenderness upon intercourse or digital examination of the vulvar area.

Overactive Bladder and Recurrent Urinary Tract Infections

Both OAB and recurrent UTIs as well as urethral syndrome and urolithiasis can cause CPP with voiding symptoms of urgency and frequency. IC is frequently misdiagnosed as being either OAB or UTI, especially when urinalysis and culture are not performed or the results are nonspecific. Clinicians should therefore suspect IC to be present among patients with these voiding symptoms who fail to respond to therapy with antibiotics or anticholinergic agents. In addition, patients with a suspected UTI who have a poor response to antibiotics should have a more thorough examination to rule out possible anatomic, metabolic, or functional abnormalities.[26]

Interstitial Cystitis

IC is an inflammatory CPPS of bladder origin that may affect as many as 1 in 4.5 women.[27] IC is characterized by urgency and frequency of urination and/or chronic perineal or suprapubic pain and pressure in the absence of a defined etiology (bladder cancer or UTI). Patients have none to severe nocturia (>12 times/night) with pelvic pain that frequently increases one week prior to menses. Dyspareunia and exacerbations after sexual intercourse are also common complaints. IC is a frequent cause of CPP. It is estimated that 80% of women with CPP — or approximately 7 million women — have pelvic pain of bladder origin.[28] IC has a high comorbidity with endometriosis and OAB and is therefore often misdiagnosed or underdiagnosed.[8] In fact, a recent study found that nearly 40% of women having a laparoscopy for suspected endometriosis were confirmed to have IC by cystoscopic examination.[8] It is therefore recommended that women who have CPP and urologic symptomatology of urgency/frequency also be evaluated for the presence IC prior to undergoing diagnostic or therapeutic surgical procedures for CPP.

Summary

CPP is a common complaint among women of reproductive age, affecting at least 9 million women in the United States.[1] A wide variety of syndromes share similar symptomatology of CPP as well as the urologic symptoms of frequency and urgency (Table 5). The etiology for the CPP is often attributed to intraperitoneal pelvic and/or urogenital causes, when in reality the source of the CPP is of bladder origin – specifically, interstitial cystitis. The high rate of comorbidity between IC and endometriosis or OAB indicates that clinicians should suspect IC to be present among women with clinical manifestations of these problems, as well as other patients who have chronic pelvic pain and urinary frequency and urgency in the absence of another defined etiology.

Table 5

SYMPTOMS OF PELVIC PAIN DUE TO GYNECOLOGIC ORIGIN ARE SIMILAR TO IC

GYN	IC
Dyspareunia	Dyspareunia
Perimenstrual exacerbations	Perimenstrual exacerbations
Exacerbations after sexual intercourse	Exacerbations after sexual intercourse
Pain: lower abdomen, vulva, urethra, vagina, medial thighs, perineum	Pain: lower abdomen, vulva, urethra, vagina, medial thighs, perineum
Voiding symptoms	Voiding symptoms

CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS

IC is a progressive but treatable condition characterized by urinary frequency, urinary urgency, and/or pelvic pain (often localized to the bladder or urethral area) in the absence of any other identifiable pathology (including UTI, bladder carcinoma, or radiation cystitis). The pathophysiology is now better understood but there are, as yet, no definitive diagnostic tests to establish the diagnosis of IC. However, there have been important advances in the diagnosis and management of IC — most notably the introduction of the Pelvic Pain Urgency/Frequency (PUF) Patient Symptom Scale and Potassium Sensitivity Test (PST) for diagnosis, and approval of oral Pentosan Polysulfate Sodium (PPS) for treatment. Recognizing that the bladder is a common source of CPP can help clinicians identify patients with suspected IC much earlier in the course of the disease, thereby limiting its potentially debilitating effect on QOL.

Interstitial Cystitis: A Historical Perspective

IC was first recognized during the 19th Century as an inflammatory pathologic entity characterized by chronic frequency, urgency, and pain in the absence of demonstrable etiology.[29] In 1914, at a regional meeting of the American Urological Association, Hunner described 8 cases of women with a history of suprapubic pain, frequency, nocturia, and urgency whose symptoms had lasted an average of 17 years. Hunner noted that, upon cystoscopy, the women had red, bleeding areas on the bladder wall that were later to become known as "Hunner's patches" or "Hunner's ulcers," but, in fact, are not true ulcers.[30] In August 1987, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) established a list of inclusion/exclusion criteria for clinical trials of IC including the presence of Hunner's ulcer or diffuse glomerulations as a required finding for diagnoses of IC.[31] However, cystoscopic studies have demonstrated that less than 10% of patients with IC are found to have "classic" (ulcerative) IC, whereas 90% of patients have no lesions demonstrated upon routine bladder inspection. In fact, Hunner's patch is usually identified only among older patients (>45 to 65 years of age) with IC who have extreme pain. Consequently, these criteria have been considered by most clinicians to be too stringent or restrictive for use in clinical practice, and many believe that use of these criteria exclude the majority of patients with IC.[32,33] Despite the absence of an accepted definition of IC, the presence of Hunner's ulcers is no longer considered necessary for the diagnosis of IC. The symptoms of CPP with voiding symptoms and absence of bacterial infection and hematuria can establish the diagnosis of IC. Nevertheless, some clinicians continue to erroneously require the presence of a Hunner's patch or glomerulations on cystoscopy for a diagnosis of IC.

Clinical Presentation of Interstitial Cystitis

CPP is described as nonmenstrual pelvic pain of 6 or more months' duration that is severe enough to cause functional disability or require medical or surgical treatment (Table 6). IC encompasses a major portion of the "painful bladder" disease complex, which includes a large group of patients with bladder and/or urethral and/or pelvic pain, as well as the presence of irritative voiding symptoms of urgency, frequency, nocturia, and dysuria, and sterile urine cultures.

Table 6

CLINICAL PRESENTATION OF INTERSTITIAL CYSTITIS

Progressive clinical condition
Non-menstrual pelvic pain of ≥6 months
Severe enough to cause functional disability or require treatment
Pain may increase 1 week prior to menses
Pain associated with sexual intercourse
Urinary urgency and frequency
Nocturia can be mild (2/night) to severe (>12/night)
Absence of any known etiology

There is a wide spectrum of symptom severity, ranging from mild pelvic discomfort and urgency/frequency to debilitating pain and severe urgency/frequency with significant nocturia (>12 times per night). Women with IC frequently report an increase in their pelvic pain and urgency/frequency during the week prior to menses; both women and men report dyspareunia or increased pain within 12 to 24 hours after sex. Some patients report that the pain increases upon bladder filling and lessens with bladder emptying, or may increase with bladder emptying. Many patients notice exacerbations associated with allergies or specific foods or beverages (especially those high in acidity), or during time of physical and/or emotional stress. Women may have stress-urge incontinence or a slow urinary stream, particularly during flares.

Epidemiology of Interstitial Cystitis

The absence of a definitive diagnosis of IC limits the ability to determine accurate incidence and prevalence data. Currently, at least 700,000 Americans are diagnosed with the severe form of IC, and it is believed that another 1 to 2 million Americans have at least mild IC (Table 7).[34,35] The majority of patients with IC are white, female patients are predominantly premenopausal, with a median age at diagnosis of 42 to 46 years.[36-38] However, most women first manifest symptomatology of IC 5 to 7 years prior to diagnosis (while they are in their 30's). In these younger women IC is frequently misdiagnosed as UTI or endometriosis.[39]

Table 7

EPIDEMIOLOGY AND DEMOGRAPHICS OF INTERSTITIAL CYSTITIS

Currently diagnosed in 700,000+ Americans[35]

- Another 1 to 2 million with at least mild IC[36,37]

Majority of patients are:

- Female
- Caucasian
- Premenopausal
- Median age at diagnosis 42 to 46 years[38]
  - Initial symptomatic manifestations 5 to 7 years earlier
  - Typically visit up to 8 clinicians before diagnosis [39]
- May be increased risk among first-degree relatives of IC patients[34]

Data from the Nurses Health Studies (NHS) (including female registered nurses aged 30 to 55 years) reported that the prevalence of IC increased from 52 per 100,000 women in 1994 (NHS-I) to 67 per 100,000 women in 1995 (NHS-II).[39] NHS-I required a diagnosis of IC by cystoscopy, whereas NHS-II queried whether the nurses had ever been diagnosed with IC. A similar population-based study in Finland determined the prevalence of IC in females to be 450/100,000.[40] Two recent studies support an earlier suggestion that as many as 1 in 4.5 women have IC: 25% of women in 8 gynecology practices had IC, and 24% of female third-year medical students had symptoms highly suggestive of IC (based on symptoms and diagnostic evaluation).[27,41,42] These study results alter the long-standing belief that IC is a rare condition.

Impact on Quality of Life

As with other CPPS, IC can significantly impair a patient's QOL. Patients often have pelvic pain that may be chronic and is frequently severe, and also have urologic symptoms that can be debilitating. Patients with severe disease can urinate more than 60 times per day, impairing not only daily activities but also the ability to enjoy a full night's sleep. QOL assessments in patients with IC are understandably consistently poor: 50% of patients with IC are unable to work full-time and 60% experience dyspareunia (Table 8).[43] Patients with IC are also at elevated risk of having emotional problems.[44] In fact, patients with IC score lower on QOL inventories than do patients undergoing dialysis.[43] The need for prompt and accurate diagnosis and treatment cannot be overemphasized.

Table 8

IMPACT OF INTERSTITIAL CYSTITIS ON QUALITY OF LIFE

Physical and psychologic impact can be profound

QOL assessments consistently poor[43]

- 50% unable to work full-time
- 60% experience dyspareunia
- Score lower than patients undergoing dialysis

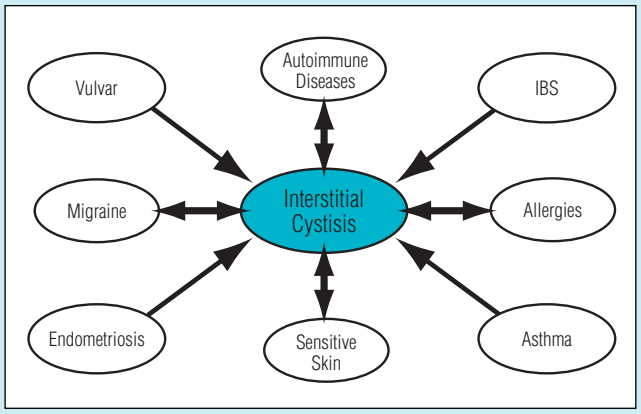
Elevated risk emotional problems[44]

Comorbidities and Pathogenesis of Interstitial Cystitis

A wide range of diseases have been associated to be present along with IC. These include allergies, migraine headache, endometriosis, inflammatory bowel disease, asthma, and sensitive skin (Figure 1). Patients with IC may have a greater chance of developing fibromyalgia, incontinence, and/or chronic fatigue syndrome. These comorbidities may eventually provide greater insight into the pathogenesis of IC, which has, as yet, no biomarker or clearly defined pathogenic cause.

Figure 1

INTERSTITIAL CYSTITIS AND ASSOCIATED DISEASES



IC is believed to have a multifactorial pathogenesis, and multiple pathologies may coexist within one patient. Numerous hypotheses have been proposed to explain the pathogenesis of IC, including the presence of (as yet unidentified) infectious mechanisms, an autoimmune response, neurophysiologic mechanisms, response to

mast cells, and changes in bladder epithelial permeability (Table 9). A recent pilot study demonstrated that first-degree relatives of women diagnosed with IC have a 17-times greater risk of developing IC than women in the general population, suggesting a possible genetic etiology of IC.[34] Some investigators have hypothesized (with no supportive data) that IC may encompass more than one disease, specifically differentiating between classic ulcerative IC and nonclassic, nonulcerative IC, although most clinicians believe these presentations represent two ends of an "IC continuum," of mild to severe.[45]

Table 9

INTERSTITIAL CYSTITIS: PATHOGENESIS THEORIES

- Autoimmune response
- Infectious mechanisms
- Mast cells
- Neurophysiologic mechanisms
- Bladder epithelial permeability (GAG layer)

Individuals that believe IC is an autoimmune response state that: (1) IC is caused by a direct autoimmune response of the bladder; (2) some of the autoimmune symptoms and pathology of IC arise indirectly as a result of tissue destruction and inflammation from other causes; and (3) autoimmune phenomena in patients with IC are coincident and unrelated to the disease. Early studies identified Tamm-Horsfall protein autoantibodies to be present in the superficial urothelium of patients with severe IC; additional studies determined that up to 50% of patients with IC have autoantibodies, suggesting that autoimmune mechanisms may have a causal or exacerbating effect upon IC.[46,47] While autoimmunity is unlikely to be the cause of disease for the majority of patients with IC, it is likely that some patients with IC will demonstrate immunologic abnormalities.

Another hypothesis suggests that the presence of bacteria or unusual organisms in bladder cells that are not yet detectable through current routine urine tests are the cause of IC. Adherents of this theory observe that a history of urinary infections is twice as common among patients with IC than the general population, and symptoms of IC can have a rapid onset. However, IC does not appear to respond to antibiotic therapies, and no unusual organisms have been identified in the bladder of patients with IC.

Despite limited data, another hypothesis under consideration involves mastocytosis. Patients with IC have increased levels of the neuroleptic substance P (SP). SP is secreted from sensory nerve endings; it transmits pain information and stimulates inflammation.[48] Patients with IC also have an increased number of pain-carrying nerves called C-fibers that carry and release SP. SP is known to trigger mast-cell secretion, particularly in the bladder submucosa.[48] Granules inside mast cells contain, among other things, histamines that can cause inflammation. Although their exact role in the pathogenesis of IC is difficult to determine, degranulated mast cells allow the abnormal release of histamines that may cause the initial insult or damage to the bladder glycosaminoglycan (GAG) layer.

A neurophysiologic hypothesis is based upon increasing evidence of hypersensitization of small sensory nerve fibers that can trigger neurogenic inflammation through the release of neuropeptides, including SP, neurokinin A, and calcitonin gene-related protein. This hypothesis may explain some of the abnormalities associated with IC, but it is unknown whether it can be considered a frequent cause of IC or just the secondary activation of sensory nerves by urinary factors.

The most commonly held theory concerning the pathogenesis of IC involves changes in epithelial permeability (Table 10). In the healthy bladder, the urothelium acts as a barrier to separate urine from the extracellular fluid; in addition, the urothelium is an active absorptive epithelium that absorbs sodium. The urothelium secretes urinary proteins such as tissue plasminogen activator and urokinase as well as protease inhibitors. Glycosaminoglycan (GAG) layers are part of the cell surface mucus composed of proteoglycans and glycoproteins that act as a barrier to the irritative substances reaching the luminal membrane; the GAG layer (mucus) is believed to: (1) inhibit bladder infections by preventing bacteria from adhering to urothelial surfaces; and (2) prevent absorption of caustic components of urine into the deeper layers of the bladder wall. Damage or alterations to the GAG layer allow transepithelial absorption of urea and potassium, eventually causing tissue damage and pain.[49] Many investigators believe that IC is the result

Table 10

INTERSTITIAL CYSTITIS PATHOGENESIS: CHANGES IN EPITHELIAL PERMEABILITY

Bladder Mucus (Glycosaminoglycans [GAG])

- Lipid and Hydrophilic barrier to luminal membrane
- Electrostatically binds water
- Prevents bacterial adherence
- Regulates urine epithelial interface

GAG permeability regulation is abnormal in interstitial cystitis

- Allows transvesical absorption of urea and potassium
- Causes tissue damage and pain

of damage to the GAG layer (mucus) enabling epithelial permeability of irritants that cause the clinical manifestations characteristic of IC.

Summary

Interstitial cystitis is a common CPPS affecting nearly 1 in 4 women. The psychological and physical ramifications of IC are profound, and patients with at least moderate IC typically have a poor QOL. The pathogenesis of IC is now better understood. IC is thought to be the result of damage or abnormalities to the epithelial GAG layer of the bladder, disrupting permeability regulation and enabling the penetration of potassium and other urine solutes, activating sensory pain and urgency fibers.

DIAGNOSIS OF IC

The diagnosis of IC has always been difficult due to the lack of histologic changes and absence of laboratory assays or biomarkers associated with the entity. In addition, some clinicians continue to adhere to the stringent NIH research criteria requiring the presence of a Hunner's patch during cystoscopy examination for a diagnosis of IC to be established. Consequently, the diagnostic process for IC has been one of exclusion – ruling out the presence of urinary tract infections, vaginal infections, sexually transmitted infections (particularly chlamydia, gonorrhea, and mycoplasma), endometriosis, and bladder cancer.

The introduction of two new diagnostic techniques – the PST and PUF – provide the clinician with office-based procedures that can easily and promptly identify patients whose CPP has a bladder component. When used in conjunction with history, physical examination, laboratory analyses, and a voiding log, clinicians can now readily diagnose and initiate treatment for IC.

Traditional Diagnostic Tests

Currently, the diagnosis of IC depends upon the presenting signs and symptoms after a differential diagnosis has been considered. The most common diagnostic techniques include history, physical examination, and a voiding log in patients who have a normal urinalysis, sterile urine culture, and negative urinary cytology (Table 11). Because less than 10% of patients with IC will have a Hunner's patch, cystoscopy (with or without hydrodistention) is not a useful diagnostic tool.

CPP of bladder origin should be considered to be present in all patients who report a history of urinary frequency and urgency and pain or discomfort in the pelvis, bladder, perineum, labia, vagina, or urethra. IC should be suspected to be present in all patients who present with cyclic or noncyclic CPP, especially if urinary urgency or frequency accompanies the pain, even in the absence of other urologic symptoms. IC should also be considered to be present in patients with: (1) symptoms of OAB, particularly among patients who do not respond to anticholinergic agents; (2) recurrent UTIs with negative urine cultures; (3) premenstrual pain or dysmenorrhea; (4) dyspareunia and/or pain surrounding sexual activity; and (5) a history (or suspicion) of endometriosis (Table 12). IC should always be considered to be present in patients with CPP and urologic symptoms prior to their undergoing diagnostic laparoscopy or other surgical procedures.

Table 11

TRADITIONAL DIAGNOSTIC TESTS

Patient history
Urinary urgency and frequency
Pelvic pain (pelvis, bladder, perineum, labia, vagina, or urethra)
Physical examination
Possible suprapubic tenderness
Possible anterior vaginal wall/bladder base tenderness
Possible rectal and/or pelvic floor spasm
Normal urinalysis, culture, cytology
Voiding log (≥8 voids/day)

Table 12

SUSPECT INTERSTITIAL CYSTITIS IN PATIENTS WITH:

- Symptoms of overactive bladder
  - Especially if no response to anticholinergics
- Recurrent urinary tract infections
- Premenstrual pain/dysmenorrhea
- Dyspareunia and/or pain surrounding intercourse
- History (or suspicion) of endometriosis

Patients with IC may have anterior vaginal wall/bladder base tenderness, rectal and/or pelvic floor spasm, or suprapubic tenderness upon digital examination. The physical examination can rule out the presence of urethral diverticula, vulvodynia, vaginitis, pelvic floor dysfunction, and uterovaginal prolapse, although it is possible for IC to coexist with any of these conditions. Gentle palpation of the bladder and urethra underneath the anterior vaginal wall may reproduce the symptoms of IC in most women. Women suspected of having IC should be asked to keep a voiding diary to record their number of daily voids. Studies have demonstrated that patients with IC void an average of 16.5 times per day, as compared with 6.5 voids per day in healthy women.[50] Eight or

more voids within a 24-hour period are consistent with the diagnosis of IC. It is not uncommon for some patients with severe IC to void more than 60 times each day.

Cystoscopy should be routinely performed on any patient with microscopic or gross hematuria and is also used to rule out abnormalities of the urethral or bladder surface. Cystoscopy may also be indicated for patients with CPP and risk factors for bladder cancer (hematuria and older age). The procedure can be performed in the office or an operating room using either a rigid or flexible cystoscope but is not required to diagnose IC. Hydrodistention of the bladder under anesthesia can illuminate petechial hemorrhages that can suggest the presence of IC; however, petechial hemorrhages have been identified in both women with IC as well as healthy women.[51] Cystoscopy with hydrodistention under anesthesia can determine the patient's maximum bladder capacity. A diagnosis of IC is supported by a finding of a small bladder capacity under anesthesia. The bladder capacity is inversely proportionate to the presence of a Hunner's patch.[37] The procedure, which is not without risk, involves: (1) filling the bladder with sterile water to a relatively high pressure; (2) emptying the bladder and the (3) inspecting the bladder mucosa for the presence glomerulation or small or large petechiae. Small ureteral tears and, very rarely, a large bladder perforation (requiring catheter drainage or open surgical repair) can occur during cystoscopy with hydrodistention. In summary, cystoscopy, with or without hydrodistention, is of limited benefit and is now uncommonly used to diagnose IC.

Evolving Diagnostic Measures

Potassium Sensitivity Test

A majority of patients with IC have an abnormality of the bladder epithelial permeability barrier that allows potassium and urea to leak into and be absorbed into the bladder interstitium causing inflammation and pain in the bladder wall. IC is now being referred to as lower urinary dysfunctional epithelium (LUDE disease). The PST was developed to identify those patients who respond with urgency or pain following the instillation of potassium into the bladder (ie, a positive PST).

The PST evolved over many years of laboratory and clinical research assessing the properties and role of the bladder mucus/GAG layer. Initial attention focused on the roles of bladder mucus in preventing bacterial adherence and as a regulator of the urine epithelial interface.[52] Early studies determined that bladder mucus, which is GAG-rich, could be removed by acid or detergent (such as protamine sulfate) and then restored through treatment with heparin or the heparinoid substance pentosan polysulfate sodium (PPS).[52] Bladder mucus was shown to reduce the interaction of urine solutes and the epithelial cell; mucus was demonstrated to have an important role in the regulation of adherence and bacterial protection. Research (on rabbits) determined that the GAG is hydrophilic and electrostatically binds water.[53] Laboratory analyses compared the normal absorption of urea, calcium, and water across bladder epithelium against their absorption levels after injury with protamine sulfate and subsequent treatment with PPS.[53] In all cases there was a significant increase in absorption levels associated with exposure to the protamine that was reduced after treatment with PPS. Additional research on 41 humans determined that either heparin or PPS could repair injury to the bladder epithelium after protamine exposure.[54] It was therefore hypothesized — and subsequently determined — that mucus (GAG) permeability regulation is abnormal in patients with IC.

Initial clinical trials compared the movement of urea in patients with normal (healthy) bladders and patients with severe IC (with and without Hunner's ulcers).[55] Normal bladders absorbed 3% to 4% of urea before injury with protamine and nearly 25% after protamine exposure. Patients with severe IC had an average 27% absorption of urea, and patients with IC and a Hunner's ulcer had an average absorption rate of 35%.

Subsequent studies examined the movement of potassium across the bladder epithelium and determined that exposure of an abnormal GAG to potassium generated symptoms of IC.[49] Potassium was found to depolarize sensory nerves and to be highly toxic in the bladder wall; in fact, an important role of the GAG layer is to protect the bladder epithelium from potassium absorption. Healthy subjects exposed to potassium after protamine injury exhibited symptoms of both urgency and pain that were reduced after heparin treatment; in contrast, exposure to sodium after protamine had little effect on pain and urgency.[49] From these numerous studies, investigators determined that the healthy bladder epithelium is relatively impermeable, protected by bladder mucus/GAG; however, injury to the GAG layer may result in gradual tissue injury to the bladder and urethra that, over time, causes pain and urinary symptoms of urgency and frequency and eventually neurological hyperactivity. The PST was originally designed to test this hypothesis, and the findings suggested its value as a diagnostic technique to help identify patients with epithelial dysfunction that results in CPP of bladder origin.

Patients with IC are often very volume sensitive — a rapid introduction of any solution into the bladder can result in significant sensory urgency. The PST involves the very slow introduction of 40 mL of room temperature sterile water into the bladder through a thin catheter, such as a low friction hydrophilic catheter, or a #10 French pediatric feeding tube used as a catheter) in the clinician's office over a 2 to 3 minute period to establish the baseline of pain perception and urgency upon bladder filling using a 0- to 5-point scale (with 5 indicating the most severe pain) (Table 13). The water is retained in the bladder for up to 5 minutes before it is emptied through the catheter, and 40 mL of KCl solution is instilled. The patient is asked to re-evaluate the level of pain and/or urgency; any increase of ≥2 points over baseline for pain or urgency indicates a positive PST. If there is no immediate reaction, the solution can be retained in the bladder for up to 5 minutes after which the catheter is removed and the patient is asked to urinate and re-evaluate the level of pain/urgency. Patients who respond to just the introduction of water are considered likely to have IC, as are patients who report discomfort with the KCl solution.

Table 13

POTASSIUM SENSITIVITY TEST (PST)

- PST measures epithelial permeability
- Healthy patients do not respond with pain/urgency to bladder instillation of H_2O or KCl
- Majority of patients with IC have positive PST (78%)
- Procedure
  - Very slow introduction of H_2O through thin catheter
  - Establish baseline of pain/urgency perception upon bladder filling
  - Retain H_2O for up to 5 minutes, empty through catheter
  - Instill KCl solution — re-evaluate level of pain/urgency
  - Any increase ≥2 points indicates positive PST
- Not sufficient alone to diagnose Interstitial Cystitis
- More specific than cystoscopy in identifying patients with suspected Interstitial Cystitis

A negative PST occurs when a patient has no pain or urgency response following instillation of both substances.

A positive PST indicates abnormal epithelial permeability and is a definitive sign that the CPP is of bladder origin.[56,57] Approximately 79% of patients with IC have a positive PST; however, other bladder diseases, including acute bacterial cystitis and radiation cystitis, can also cause a positive PST and their presence should be ruled out.[58] In contrast, less than 3% of healthy individuals have a positive PST.[58] Recent studies have shown that approximately 85% of gynecology patients who complain of CPP have a positive PST often, despite the presence of other initial diagnoses.[27,28] A positive PST demonstrates epithelial dysfunction, aiding in the diagnosis of IC, but a negative PST does not rule out IC, as false negatives can occur.

The PST can be performed by nonurologists on an outpatient basis, unlike cystoscopy with hydrodistention. The PST can cause immediate but short-lived discomfort or flare-ups of the disease, but symptoms generally subside within minutes. The PST cannot be used to inspect the bladder wall or perform a biopsy. It is not sufficient in and of itself to diagnose IC, but this technique identifies significantly more patients with IC than does cystoscopy. In summary, the PST is a highly specific (98%) and sensitive (~80%) diagnostic technique that, when combined with history, a negative laboratory analyses, and physical examination, can identify the overwhelming majority of patients with IC.

Pelvic Pain and Urgency and Frequency (PUF) Patient Symptom Scale

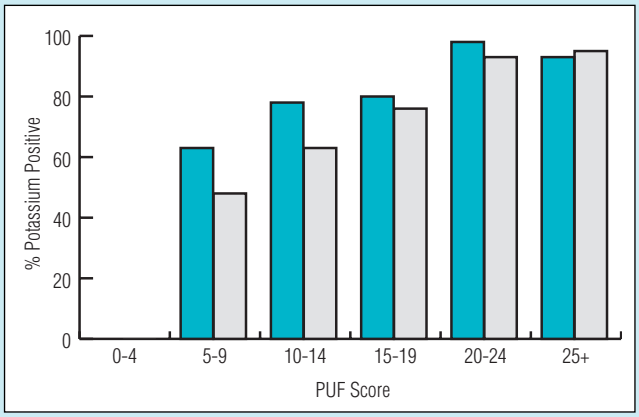
The PUF measures the presence and severity of IC symptoms, as well as the degree to which patients are bothered by the symptoms (Figure 2, inside back cover). This 8-question symptom scale requires only approximately 5 minutes to complete and assesses both genitourinary and gynecologic symptoms together in one simple diagnostic test. The questionnaire gives equal weight to the three primary symptoms of IC: frequency, urgency, and pain; with two questions that address symptoms following sexual activity. The maximum score on the PUF is 35; nearly all healthy women have low PUF scores (≤2 points). Total scores of ≥8 points indicate a high probability that the patient has IC. Recent studies have found that patients with a PUF score of 5 to 9 have a 55% likelihood of having IC, and those with a score of 10 to 14 have a 74% likelihood of IC.[27] The PUF can readily distinguish IC from other abdominopelvic conditions, including UTI and gynecologic causes of CPP. It has been recommended that the PUF questionnaire should be routinely administered to all patients who complain of CPP; all patients with a PUF score of at least 5 should be suspected of having IC and treated appropriately.

Potassium Sensitivity Test + Pelvic Pain Urgency Frequency Patient Symptom Scale = Highly Effective Diagnostic Paradigm

There is a strong correlation between the PUF and PST tests: high PUF scores correlate highly with a positive PST in both male and female patients suspected of having IC.[27] Ninety-one percent of patients with a PUF score >20 have a positive PST, as do 76% of patients with a score of 15 to 19 and 55% of patients with a PUF score of 5 to 9 (Figure 3).[27] In comparison, control women nearly always have low PUF scores (<2) and 0% positive PST results. These findings confirm the value of the PUF as an effective initial diagnostic technique to screen patients who present with CPP. In addition, the high correlation between the two diagnostic tests may eventually enable clinicians to reserve the PST for those

Figure 3

PUF SCORES AND POTASSIUM-POSITIVE REACTION GYN vs GU[27]



PUF=pain/urgency/frequency, blue=GYN grey=GU

patients who present with symptoms suggestive of IC but whose PUF scores are intermediate (5 to 10).

Promising Clinical Markers

Two promising clinical markers are under investigation for the diagnosis IC. The first utilizes the finding that patients with IC have significantly lower levels of the urinary glycoprotein GP51 than normal individuals; the second reflects the presence of Antiproliferative Factor (APF) in a majority of patients with IC but not in patients with other urogenital disorders.[59-62] APF inhibits proliferation of bladder epithelial cells and complex changes in epithelial growth factor levels.[60,61] Studies are examining the role of APF in the pathogenesis of IC, and investigators are exploring its potential value as a marker for IC.[60]

Summary

Until recently, IC was a difficult condition to diagnose. The stringent research inclusion criteria established by the NIDDK required the visualization of Hunner's patch or glomerulations during cystoscopy, thereby eliminating at least 60% of patients with IC. Recent additions to the diagnostic modalities – particularly the PST and PUF – can readily identify patients whose CPP is of bladder origin. Diagnosis of IC can be determined with a positive PST and/or a PUF >5 when used in conjunction with history, physical examination, and a voiding log for patients with CPP who have normal urinalysis, sterile urine culture, and negative urinary cytology.

STRATEGIES FOR MANAGING INTERSTITIAL CYSTITIS

Problems for clinicians have resulted from the historical absence of effective therapies for the management of IC. In fact, the Interstitial Cystitis Data Base Study Group (ICDS) recorded 183 different types of therapy for the nearly 600 women enrolled in the study, and nearly half of the women received a combination of at least two treatments.[63] The therapeutic principles of IC therapy are based upon the three most common hypothesized pathophysiologies underlying this condition: (1) treat the damaged GAG layer (mucus) of the epithelium; (2) treat related allergies; and (3) treat the neural up-regulation of pain and sensory nerves (Table 14). Patients with long-standing, of at least moderate disease may require a multimodal approach that integrates all three therapeutic principles.

Table 14

PRINCIPLES OF INTERSTITIAL CYSTITIS THERAPY

Treat the damaged GAG epithelium
Treat related allergies
Treat neural up-regulation

Nonpharmacologic approaches — particularly diet and behavioral therapies — are often recommended to enhance the benefits of pharmacologic treatments, but are rarely sufficient when used as monotherapy. For many years, the only treatment approved by the Food and Drug Administration (FDA) for the management of IC was bladder instillation with dimethyl sulfoxide (DMSO), a moderately effective and safe, albeit invasive, procedure. The approval in 1996 of PPS provided patients with IC with an effective and safe oral regimen that specifically targets and repairs the damaged urothelium. An evolving treatment approach utilizes oral PPS as the foundation of multimodal therapy, in combination with a variety of adjunctive pharmacologic and nonpharmacologic therapies to provide enhanced pain and symptomatic relief.

Nonpharmacologic Approaches

Nonpharmacologic therapeutic modalities for IC include alterations to the diet and/or behavioral techniques (Table 15). Neither modality is sufficient alone, particularly for patients with at least moderate disease; however, these approaches can supplement pharmacologic therapies to enhance symptomatic relief and disease remission. Diet modification includes the avoidance of foods found (at least anecdotally) to exacerbate IC symptoms: most notably, foods high in potassium (alcohol, tomatoes, chocolate) or caffeine. Patients with severe disease should be told to initially alter their diet followed by slowly adding back individual foods from the restricted list depending upon the resumption of symptoms.

Table 15

NONPHARMACOLOGIC THERAPEUTIC INTERVENTIONS

Diet Modifications — Remove foods that may exacerbate symptoms
High in acidity (tomatoes, alcohol, chocolate)
Caffeine
Artificial sweeteners
Behavioral Interventions
Bladder-training techniques
Relaxation/distraction techniques
Voiding diary
Pelvic floor relaxation exercises

Behavioral therapies include bladder-training techniques, internal (pelvic floor) massage, relaxation and distraction techniques, and pelvic floor relaxation exercises (with or without biofeedback training). These techniques may provide a quick response among patients with early (mild) IC, but are less effective for patients with long-standing disease.[50] Patients with IC have been shown to void an

average of 16.5 times per day, in comparison with 6.5 voids per day among healthy patients.[64] The use of scheduled voiding patterns can help patients gradually increase the time interval between voids until they can be spaced at least 3 to 4 hours apart. Patients should also be asked to keep a voiding diary to help record improvements against baseline. Bladder training is often supplemented with relaxation and distraction techniques to help the patient maintain the voiding schedule; physical therapy can teach the patient how to perform gentle stretching and pelvic floor relaxation exercises, as well as biofeedback.

Pharmacologic Therapeutic Modalities

FDA-Approved Treatments

Oral Pentosan Polysulfate Sodium (PPS)

Pentosan polysulfate sodium (PPS) is the first and only *oral* drug approved by the FDA for the management of bladder pain or discomfort associated with IC.[65] PPS is a heparinoid compound similar in chemistry and structure to the naturally occurring GAGs produced in the urinary epithelium (Table 16).[53] PPS is believed to act primarily by replenishing the defective GAG layer and inhibiting inflammatory processes in a way that has been likened to the effect of Pepto-Bismol® on gastrointestinal distress.[66] Specifically, PPS acts as a buffer to control cell permeability and prevent irritating solutes from reaching epithelial cells: PPS coats the epithelium and secondarily reduces the inflammation. PPS may also have a stabilizing effect on mast cells and is thought to detoxify cations in urine that could injure the anionic bladder mucus.

Table 16

PENTOSAN POLYSULFATE SODIUM

- First oral drug approved for Interstitial Cystitis
- Similar in chemistry/structure to GAG
- Mechanisms of Action
  - Replenishes defective GAG layer
  - Inhibits inflammatory processes
  - Coats the epithelium, soothes the inflammation
- Dosage: 300 mg/day (3-100 mg capsules) for at least 2 to 4 months
  - Recommended duration 6 months or more

The current FDA-recommended dosage is 300 mg/day taken as a 100-mg capsule three times per day; an evolving regimen (for enhancing compliance) utilizes 200 mg twice daily.[41,67] PPS works slowly and methodically to repair the damaged urothelium; as such, the recommended course duration is at least 2 to 4 months for patients diagnosed early in the disease process (mild-to-moderate IC), and at least 6 months for patients with moderate to severe disease, although some patients may not notice significant symptomatic improvement until at least one year of treatment.[68] Patients who have severe disease, disease of long-standing, or increased urinary frequency often require treatment for 6 to12 months or longer. It is therefore recommended that all patients receive treatment for a minimum of 6 months.

PPS is a well-tolerated Category B agent with no drug-drug interactions. There may be infrequent, mild and transient side effects including minor gastrointestinal discomfort (diarrhea, nausea), localized alopecia, and headache (Table 17).[65] Approximately 1% of patients treated with PPS experience slight liver function changes; these have not been associated with jaundice or other clinical signs or symptoms, and usually resolve spontaneously. Finally, PPS has no impact on coagulation profiles.

Table 17

PPS: MINIMAL SIDE EFFECTS[65]

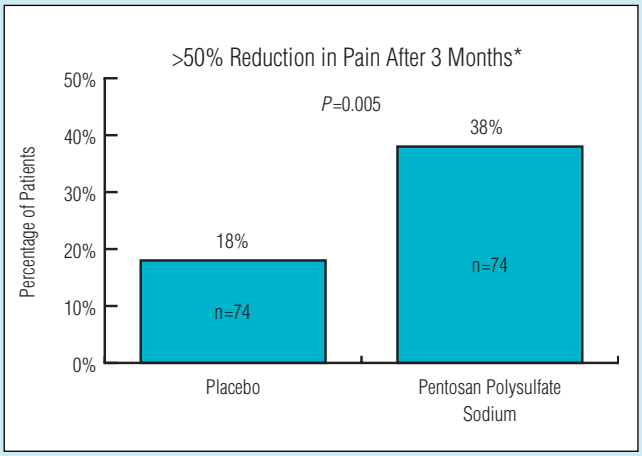
- No drug-drug interactions
- Adverse events infrequent, mild, transient
- Most frequent adverse events (1% to 4%)
  - Diarrhea
  - Nausea
  - Localized alopecia (reversible upon discontinuation)
  - Headache
  - Rash
  - Abdominal pain
  - Minor liver function abnormalities (~1%)
  - Dizziness

The efficacy of PPS in reducing IC-associated pain has been demonstrated in three double-blind, placebo-controlled clinical trials.[69-71] An early study involving 62 patients diagnosed with IC demonstrated statistically significant subjective improvements in pain (P=.02), urinary urgency (P=.03), frequency (P=.05), and nocturia (P=.05) after PPS treatment 100 mg three times per day for 4 months compared with placebo or baseline.[69] Patients also reported statistically significant subjective improvement in average voided volumes (P=.009), although there was no significant difference in the average number of daily voids. A multicenter, double-blind trial randomized study of 110 patients with long-term (>1 year) IC who had failed other treatments (including intravesical DMSO therapy) utilized either placebo or PPS(100 mg 3 times daily) for 3 months.[70] More than twice as many patients receiving PPS as placebo noted moderate improvement relative to baseline (28% vs 13%, respectively; P=0.04) including reduced pain (27% PPS vs 19% placebo, P=0.08) and reduced pressure to urinate (22% PPS vs 11% placebo, P=0.08). Patients receiving PPS also had a greater

increase in bladder capacity (volume per void) than did recipients of placebo, and 26% of PPS recipients reported good or better overall improvements compared to 11% of placebo recipients (P=0.03).[70] Finally, a non-randomized, long-term, open-label study involving >2800 patients with IC investigated the efficacy of PPS (100 mg 3 times/day for 3 months or more).[71] At least moderate improvement in pain relief was reported by approximately half of the patients who continued PPS therapy for at least 3 months duration; maximum benefit in pain and urgency was noted after 6 to 11 months of treatment that persisted for at least 3 years. These findings were substantiated in a 12-week, double-blind, randomized trial that significantly demonstrated the efficacy of PPS versus placebo for the reduction of pain associated with moderate to advanced IC (Figure 4).[68]

Figure 4

PPS DEMONSTRATES SIGNIFICANT IMPROVEMENT OF SYMPTOMS[68]

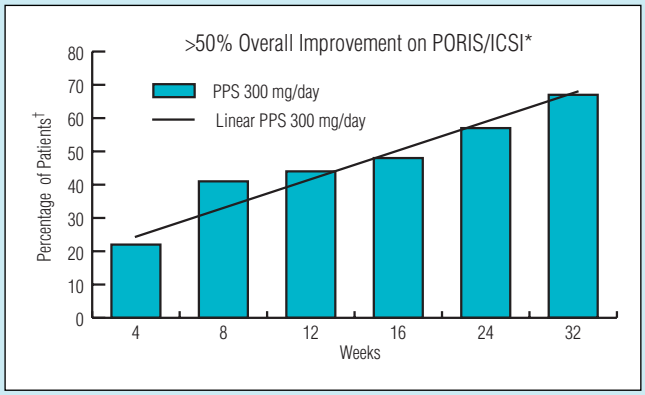


*Results from double-blind, randomized, placebo-controlled trial. Data taken from Patient Self-Evaluation.

A dose-ranging study of PPS demonstrated that symptomatic improvement increases with duration of dose, but found minimal difference between the 3 dosage groups on exit scores for pain and urgency.[72] The 377 patients in the trial had a PST at trial entry and completion, and rated their symptoms using the Patient Overall Rating of Improvement in Symptoms (PORIS) scale after PPS treatment with 1 of 3 doses: 300, 600, or 900 mg/day. Nearly 80% of the 198 patients who completed the 32-week trial had a positive PST at study entry, and 60% reported a clinical improvement at study completion with highly significant improvements in both pain and urgency symptoms.[72] PPS treatment led to ≥50% improvement on the PORIS scale in 74.1% of patients (Figure 5).[72] This study also found that PPS treatment significantly reduces potassium sensitivity as measured by the PST. The study provided evidence for the significant therapeutic benefits of long-term therapy with PPS.

Figure 5

PPS – SYMPTOMATIC IMPROVEMENT INCREASES WITH DURATION OF DOSE[72]



*Assessing pain, urgency, frequency, nocturia.
†Completers.

In summary, PPS is an effective oral treatment that usually reduces the pain and bladder symptoms associated with IC, particularly when used for at least 6 months. The excellent safety of PPS and lack of drug-drug interactions enables long-term use, which then facilitates longer remissions. PPS use should therefore be considered as the foundation of therapy for all patients who manifest symptoms suggestive of IC.

Intravesical Dimethyl Sulfoxide (DMSO)

DMSO (RIMSO-50, a 50% aqueous solution of DMSO) is an anti-inflammatory analgesic with muscle-relaxing properties (Table 18). For nearly 30 years, DMSO has been the only FDA-approved bladder instillation treatment for PPS. While the mechanism of action remains unknown, DMSO is believed to increase reflex firing of pelvic nerve efferent axons and to increase bladder capacity.[73,74] DMSO also

Table 18

DIMETHYL SULFOXIDE

- First/only agent approved for bladder instillation
  - DMSO
  - RIMSO-50 (50% aqueous solution of DMSO)
- Anti-inflammatory analgesic
- Muscle-relaxing properties
- Mechanism of action unknown[73,74]
  - Increases reflex firing of pelvic nerve efferent axons
  - Increases bladder capacity

releases nitric oxide from afferent neurons and may inhibit mast cell secretion.[75,76] However, DMSO has no known effect on the underlying cause of IC (abnormalities in the GAG layer), and it can produce a garlic-like taste and/or odor on the breath or skin that persists for up to 72 hours after treatment.[77] Patients receiving DMSO therapy are advised to have kidney and liver function tests every 6 months. Consequently, clinicians are utilizing this therapy less frequently than in prior years.

Intravesical instillations of DMSO are administered either once weekly or every other week for 6 to 8 weeks, either by a clinician in the office or by the patient at home through self-catheterization.[78] The procedure involves the insertion of a catheter into the bladder through which a solution of DMSO is passed and retained for approximately 15 to 20 minutes before expelled (Table 19). The procedure can be painful, and it may be difficult for patients with more severe disease to retain the solution for the recommended 20 minutes. Nevertheless, most patients treated with DMSO report a favorable response to the treatment within 3 to 4 weeks after initiation of the first 6 to 8 week treatment course.

Table 19

BLADDER INSTILLATION WITH DMSO

- In-office or self-catheterization
- Treatments administered once/week or once every other week
- Each treatment course = 6 to 8 weeks
- Procedure
  - Insertion of catheter
  - DMSO passed into bladder and retained for ~15 minutes
- Adverse effects: garlic-like taste/odor on breath/skin
  - Blood testing every 6 months

Most patients experience at least moderate symptom relief and an increase in bladder capacity with DMSO treatments (Table 20).[74,76,79,80] Intravesical administration of DMSO every 2 weeks for 2 sessions (for a total of 4 treatments) was compared with the same regimen using saline placebo; 93% of the DMSO recipients compared with 35% of placebo recipients reported objective improvement, with 53% of DMSO versus 18% of placebo recipients reporting marked improvement.[79] Another trial reported that 74% of patients with ulcerative IC who were treated with DMSO reported satisfactory symptomatic relief, and 80% of the 46 patients experienced an increase in bladder capacity.[74] A trial of patients with chronic inflammatory bladder disease had ambiguous results — 80% of the patients reported satisfactory symptomatic relief, but there was no post-therapy evidence of significant alterations in the morphologic appearance of the bladder visualized cystoscopically.[80]

In summary, clinical trials indicate DMSO treatments are at least moderately effective. For patients with severe symptoms,

Table 20

DMSO EFFICACY

Patients (N)	Treatment	Findings for DMSO
33[79]	DMSO 50% every 2 weeks, for 2 sessions	93% of subjects experienced objective improvement. 53% of subjects experienced subjective improvement.
30[80]	DMSO	80% of subjects experienced satisfactory symptom relief. No morphologic changes on endoscopy.
46[74]	DMSO	75% of subjects experienced satisfactory symptom relief. 80% of patients experienced increased bladder capacity.
12 women[76]	DMSO, 3 to 6 treatments	50% to 77% of subjects experienced symptom relief.

DMSO can be combined with heparin and/or lidocaine.[44,81] However, remissions associated with DMSO therapy are rarely complete, necessitating additional treatment courses that usually reduce the duration of remissions of pain.[82,83]

Alternative Treatment Options

Second-Line Oral Therapies

A wide range of oral therapies can be used in conjunction with oral PPS or intravesical DMSO to provide additional relief from the pain and urologic symptoms of IC (Table 21). Patients with an allergy component to IC may be given antihistamines,

Table 21

SECOND-LINE ORAL THERAPIES

Antibiotics	Anticholinergics
Antihistamines	Analgesics
Antidepressants	Antiepileptics

particularly hydroxyzine hydrochloride (25 to 75 mg) at night to alleviate nocturia and help with sleeping. A recent study demonstrated that hydroxyzine (75 mg/day for 3 months) alleviated IC symptoms in 40% of patients and in 55% of patients with a history of allergy.[84] Analgesics, including aspirin and nonsteroidal anti-inflammatories (NSAIDs), may be utilized to help alleviate mild discomfort by inhibiting prostaglandin synthesis. However, it should be noted that NSAIDs may release histamines and can potentially exacerbate symptoms of IC. Some patients with severe pain may require opioid analgesics (eg, acetaminophen with codeine).

Antibiotics are prescribed when there is objective evidence of concurrent UTIs with bacteria present, not just white blood cells which can be due to a non infection inflammatory response. Similarly, anticholinergics are frequently recommended for patients with concomitant OAB or with severe urgency/frequency. Other second-line therapies include antispasmodic agents such as hyoscyamine sulfate; the anti-epileptic agent gabapentin; and antidepressants, particularly amitriptyline and other tricyclic antidepressants (TCAs).[85] TCAs decrease norepinephrine and serotonin reuptake in the central and peripheral nervous system, facilitating pain relief, and also inhibit histamine secretion from mast cells. Amitriptyline has anticholinergic properties that can help reduce nocturia and urinary frequency when administered at a nightly dosage of 10 to 75 mg.[86] Studies have shown that 60% to 90% of patients report pain reduction with amitriptyline; however, this agent can cause cardiac irregularities and constipation and should therefore be recommended to be used with caution and low initial doses which can be gradually increased.[86,87]

Other Intravesical Agents: Heparin

Heparin is a sulfated polysaccharide similar to those found in the GAG/bladder epithelium. It has beneficial anti-adherence action that protects the bladder mucosa against bacterial invasion.[88] Intravesical instillation of heparin is believed to correct the underlying mucosal defect associated with IC, thereby restoring the injured urothelium. Although it is not FDA-approved, intravesical heparin has been used as both monotherapy and in combination therapy with generally favorable results, affording patients relief from their symptoms and prolonged remissions of IC.[89,90]

Initial studies found that intravesical heparin (10,000 units in 10 mL of sterile water 3 times per week for 3 months) provided clinical remissions in 56% of patients with IC.[89] Continued therapy (for 3 to 9 months) maintained the remissions.[89] More recent studies demonstrated that 75% of women with IC or frequency/urgency syndrome who received intravesical heparin therapy (25,000 units twice/week X 3 months) reported >50% improvement in symptom scores, that was then confirmed by urodynamic studies.[90] Additional studies have supported the beneficial effects of heparin when used in conjunction with intravesical DMSO treatment: the combination therapy reduces the relapse rate and facilitates extended remissions.[73,91] Heparin may have a greater dose-dependent effect on blocking adenosine triphosphate release than DMSO, with the potential to afford greater relief from symptoms than DMSO.[92]

Anesthetic Intravesical Solutions: "Therapeutic Cocktails"

Anesthetic intravesical solutions — "therapeutic cocktails" — are a recent addition to the therapeutic armamentarium for IC. The therapeutic cocktails can provide immediate temporary relief of urgency/pain associated with IC; each instillation can provide relief that lasts for hours to days. This procedure, which can be performed by patients at home, may be particularly beneficial for those with severe disease or for patients beginning oral PPS therapy.[58,93] A recent study demonstrated that 85% of IC patients reported sustained pain relief when treated 3 to 7 times per week for at least 2 weeks.[93]

These intravesical solutions combine either PPS (1 or 2 100 mg capsules dissolved in 10 mL buffered normal saline) or heparin (10,000 to 40,000 units) as the active agent along with 3 mL 8.4% sodium bicarbonate and 8 mL 2% lidocaine (Table 22).[58,81,89,93-95] Use of PPS provides a significant cost savings compared with the cost of intravesical heparin. Intravesical absorption of lidocaine is significantly increased with the addition of sodium bicarbonate.[96] The therapeutic solution is instilled into an empty bladder using either a low friction hydrophilic catheter or a #10 French pediatric feeding tube while the patient in the dorsal lithotomy position; the patient is asked to retain the solution for up to 30 minutes. In addition to being safe and effective, anesthetic intravesical solutions often provide patients who have severe disease with an immediate avoidance of pain.

Table 22

ANESTHETIC INTRAVESICAL SOLUTIONS ("THERAPEUTIC COCKTAILS")

- Can provide immediate temporary relief of urgency/pain
- Beneficial for patients:
  - With severe disease
  - Beginning oral PPS therapy
- Either PPS (100 to 200 mg) or heparin (10,000 to 40,000 units)

+

3 mL 8.4% $NaHCO^3$

+

16 mL 2% lidocaine

Instilled with a low friction hydrophilic catheter or a #10 French pediatric feeding tube.

Cystoscopy With Hydrodistention

Cystoscopy with hydrodistention is primarily a diagnostic technique that can help confirm a diagnosis of severe IC. This procedure has also been shown to have therapeutic benefits in 30% to 60% of patients with IC.[97] After an initial temporary period during which symptoms typically worsen,

patients with less severe disease may experience relief from symptoms of IC following cystoscopy with hydrodistention under anesthesia. However, the procedure is rarely (if ever) performed solely for therapeutic purposes.

Surgery

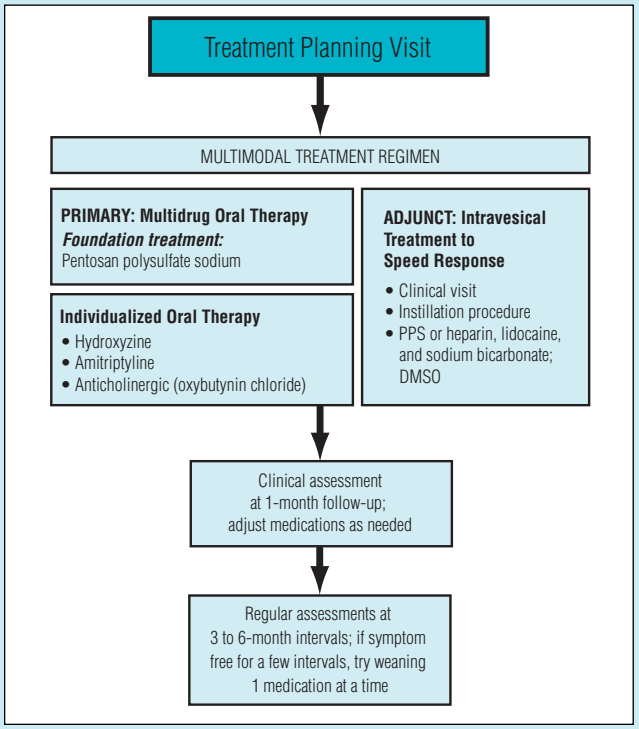
Surgery is used only as a last resort. While symptoms may initially improve dramatically after surgical removal of Hunner's ulcers, the pain and ulcers often recur within 1 to 2 years. Bladder augmentation is to be discouraged because it offers no pain or urgency relief. Finally, cystectomy (removal of the bladder) may be performed in those very rare patients with very severe disease for whom all other forms of treatment are ineffective.

Treatment Protocol For Interstitial Cystitis: A Multimodal Therapeutic Approach

Patients who are diagnosed early in the disease process may respond quickly to monotherapy with oral PPS. However, a multimodal treatment approach is often necessary for patients with severe and/or long-standing disease (Figure 6). Oral PPS is the foundation for the therapeutic protocols in order to treat the underlying pathogenic problem; however, patients with severe disease usually will not experience symptomatic relief with oral PPS for at least 2 months. Consequently, anesthetic intravesical solutions may be indicated to provide immediate, albeit temporary, pain relief during the initial months while the oral PPS begins to repair the damaged urothelium. On an individualized basis, adjuvant oral therapies, including analgesics, anticholinergics, amitriptyline, or antihistamines, may be recommended for short durations. Nonpharmacologic approaches can be used to augment and speed the recovery process. The first follow-up after diagnosis and treatment initiation can be scheduled for 8 to 12 weeks later, and medications can be adjusted then as needed. Subsequent follow-up visits can be scheduled at 3- to 6-month intervals. Regular follow-up visits should be scheduled for at least 1 to 2 years after treatment initiation. It should be noted that all of the diagnostic and therapeutic procedures for IC have Current Procedural Terminology (CPT) codes for reimbursement (Table 23, page 16).[98] Finally, education and counseling should be an integral component of the therapeutic approach to help patients establish realistic expectations for the treatment. Nursing and support staff can be utilized to administer and score the PUF and PST, as well as provide written materials and referrals to patient support groups.

Figure 6

TREATMENT PROTOCOL FOR INTERSTITIAL CYSTITIS



DMSO = dimethyl sulfoxide
IC = interstitial cystitis

Adapted from Dell JR: Oral and Intravesical Management of Interstitial Cystitis: Practice Strategies for Successful Outcomes. *Pract Building Today* 2003:4-11.

Summary

The management of IC need no longer be a challenge for clinicians and other women's health care providers. Suspicion of bladder origin of CPP can help identify patients with IC early in the disease process, facilitating an enhanced prognosis with appropriate treatment. Women with early/mild IC may only need monotherapy with oral PPS or intravesical DMSO, possibly in conjunction with nonpharmacologic interventions, for durations of up to 6 months. However, women who are diagnosed later in the disease process with ongoing and/or moderate to severe symptoms frequently require longer duration therapy. As a general rule, at least 1 month of treatment should be administered for every year that a patient has had the disease (with or without the accurate diagnosis). A multimodal approach is often recommended, using oral PPS as the foundation to repair the underlying bladder defect. IC is a chronic disease; it may take months for symptom relief, but stopping the PPS therapy usually results in relapse of symptoms. Adjuvant oral therapies can provide additional relief from the chronic pain and urologic and/or allergic symptoms.

CHRONIC PELVIC PAIN OF BLADDER ORIGIN IN MEN: THE RELATIONSHIP BETWEEN NONBACTERIAL PROSTATITIS AND INTERSTITIAL CYSTITIS

Overview of Chronic Prostatitis/Chronic Pelvic Pain Syndrome

In 1998, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes

Table 23

APPROPRIATE CPT CODES FOR INTERSTITIAL CYSTITIS[98]

Purpose of Visit/Procedure	CPT Code(s)
• New patient (comprehensive)	99204/99205
• Established patient (detailed or comprehensive)	99214-99215
• Initial consult (Level 4 or 5)	99244 or 99245
• Follow-up Visits (1st and 3rd month)	99213/99214
• Second opinion	99274 or 99275
• Urinalysis	8100
• Cytology	88151
• Urine culture	87086, 87088, P9612, 87181/87184
• Cystourethroscopy	52000
• Urethral/bladder catheterization (simple)	51701
• Bladder Instillation	51700
• PST solution	J3480
• Therapeutic Solution*	J1644 for heparin, J2000 for lidocaine, J1212 for DMSO
• Bladder irrigation, Simple and/or instillation	51700
• Nonimaging Pelvic Ultrasound	51798
• Cystoscopy	52000
• Hydrodistention	52260
• Catheter supplies	A4353

*Solution also includes 10mL of 1% lidocaine or 16 mL of 2% lidocaine and 3mL of 8.4% sodium bicarbonate (not billable). PPS, 100-200 mg (not billable) may be substituted for heparin. (Note: intravesical use of PPS in an off-label use of this product)

of Health (NIH) classified prostatitis into four distinct categories.[99] Category I and Category II prostatitis encompass acute and chronic bacterial prostatitis (respectively), and Category IV prostatitis, or asymptomatic inflammatory prostatitis, is diagnosed when a patient has no symptoms but white blood cells are found in the semen, prostate secretion or prostate tissue, most frequently during examinations for infertility or prostate biopsy. The most common classification is inflammatory or noninflammatory Category III, Chronic Nonbacterial Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) – defined as chronic (>3 months) genitourinary pain in the absence of traditional uropathogens localized to the prostate gland and detected by traditional culture techniques.[100] At least 90% to 95% of men with chronic prostatitis are ultimately diagnosed as having CP/CPPS.[101,102] Regardless of whether the etiology is bacterial or nonbacterial, the impact of CP on QOL is profound — studies indicate it is at least comparable to, if not worse than, that of myocardial infarction, angina, or Crohn's disease.[103] As with IC in women, prompt diagnosis and appropriate treatment for men with CP/CPPS can limit its physical and psychological consequences.

CP in men is a common diagnosis with an overall prevalence estimated at 9% in the United States (Table 24).[104] CP accounts for greater than 8 million outpatient visits per year and is among the 5 most common urologic diagnoses in men < 50 years of age.[105,106] The overwhelming majority (>90%) of men diagnosed with CP are urine culture-negative,

Table 24

CP/CPPS: MAGNITUDE OF THE PROBLEM

- Overall prevalence of CP: ~9%[104]
- ~8 million outpatient visits in US/year[105]
- Among 5 most common urologic diagnoses in men <50 years[106]
- ≥90% CP patients are urine culture-negative[106]
  - Only 5% - 10% of prostatitis cases are bacterial[100,106]
  - Consider pain of bladder origin

and although these patients are traditionally treated with antibiotics, most have never demonstrated a positive pathogen.[100,106] In fact, only 5% to 10% of cases of prostatitis have a bacterial etiology.[106,100] One consideration for these patients is that their (referred) pain may actually be of bladder — and not prostate — origin, specifically IC.

Interstitial Cystitis in Men: Clinical Presentation

CPP of bladder origin should be suspected in men who present with voiding symptoms (urinary urgency or frequency), painful voiding, and/or nocturia; or pelvic

pain (generalized, or pain associated with sexual activity, bladder filling and/or post-void). This clinical presentation is similar to that of CP/CPPS – in fact, IC is most commonly diagnosed initially as chronic non-bacterial prostatitis (Table 25).[107] Initially, men report suprapubic discomfort, dysuria, urgency and frequency, and nocturia; these symptoms increase in severity within a short duration. Sexual dysfunction, and particularly painful ejaculation, is a common complaint with moderate to severe IC. Nearly half (45%) of men diagnosed with non-inflammatory CP/CPPS have pain with bladder filling during urodynamic evaluation, another symptom characteristic of IC.[107] Clinicians should therefore always consider the possibility of an urothelial origin for pelvic pain in patients with unresolved CP/CPPS.

Table 5

INTERSTITIAL CYSTITIS AND CHRONIC PROSTATITIS MAY BE NEARLY IDENTICAL IN CLINICAL PRESENTATION[53]

Symptom	IC	Chronic Prostatitis
Voiding symptoms (frequency, urgency, nocturia)	✓	✓
Food often affects symptoms	✓	✓
Pain (generalized*, pelvic, with intercourse, on bladder filling, and postvoid)	✓	✓
Glomerulations often noted upon hydrodistention	✓	✓

*Perineal, medial thigh, rectal, lower back, lower abdomen.

Pathogenesis of Interstitial Cystitis in Men

The proposed pathogenesis of IC in males is similar to that of females and focuses on a deficiency in the mucosal barrier glycosaminoglycans (GAG), mast cell inflammation, and neurogenic inflammation with Substance P.[48,53,108] It is, as yet, unknown what causes the initial insult to the bladder — hypotheses include an initial UTI, or insult to or inflammation in the prostate. The GAG layer extends into the prostatic urethra in men. As such, epithelial dysfunction has been identified not only in the bladder but also in the prostate and urethra, suggesting that IC and CP/CPPS may be better described as part of a lower urinary dysfunctional epithelium (LUDE).[56,58,109,110]

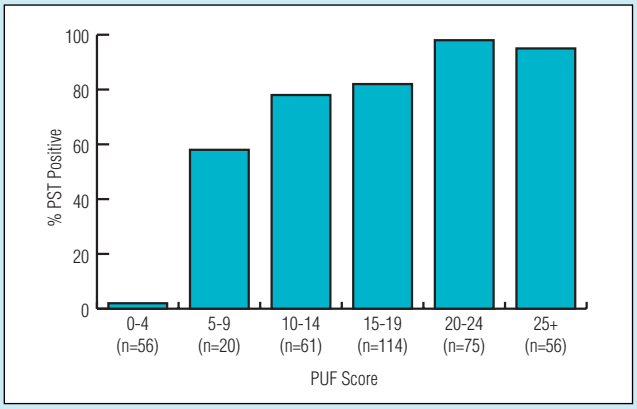
Diagnosing Interstitial Cystitis in Men

The diagnosis of IC is similar for men and women, including history, physical examination, and laboratory tests. In addition, the PST and symptom-specific questionnaires (such as the PUF) are often helpful in identifying men with possible IC. The most common physical findings include suprapubic tenderness and anterior rectal wall tenderness upon digital rectal examination (DRE); some patients report testicular pain in the absence of objective findings. Bacteriologic studies are negative, and urodynamic studies consistently demonstrate low flow rates with small post-void residual.

The PST appears to be a good predictor of IC in both women and men.[27,49,109,110] In a recent multicenter study, greater than 80% of men with IC had a positive PST, and 84% of men with prostatitis had positive PST results.[72,110] The high correlation between high PUF scores and a positive PST seen in women is also observed in men with IC (Figure 7); some clinicians therefore recommend that the PUF be administered to all males with symptoms suggestive of CP/CPPS.[27] The PST may therefore be reserved for patients whose clinical presentation suggests IC but who have low (<5) PUF scores.

Figure 7

HIGHER PUF SCORES CORRELATE WITH INCREASED PST-POSITIVE REACTION[27]



n=334 patients. 48 normals.

Management of Interstitial Cystitis in Men

The Role of Oral Pentosan Polysulfate Sodium (PPS)

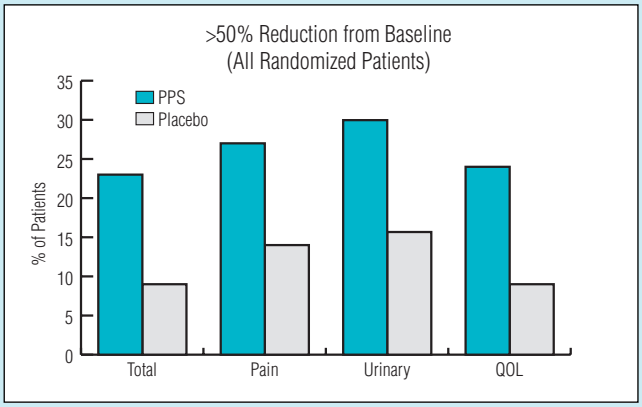
Despite the absence of a demonstrated bacterial etiology, CP/CPPS (due to misdiagnosed IC) has traditionally been treated — unsuccessfully — with empiric antibiotics. Studies have demonstrated the efficacy of oral PPS upon symptoms of CP/CPPS and/or IC and found a beneficial influence on the pain as well as on systemic effects, particularly arthralgia and myalgia.[111-113]

In a prospective multicenter Phase II study, 32 men diagnosed with moderate to severe CPPS Category IIIA were treated with PPS 100 mg tid for 6 months.[112] Nearly half of the men reported a >50% decrease in symptom score with PPS therapy (Abstract). In a double-blind, placebo-controlled trial, 100 men with CPPS received either PPS 300 mg TID (n=51) or placebo (n=49) for 16 weeks, followed by another 16 weeks open-label phase.[113] Treatment with PPS led to significant reductions in pain and improvements in QOL after 12 weeks compared with placebo, as well as a >50%

reduction in NIH-Chronic Prostatitis Symptom Inventory (CPSI) scores (Figure 8). PPS was well tolerated and led to significant clinical global improvement (P=0.04) in patients with CPPS when compared to placebo therapy. These findings suggest that oral PPS can be used to safely and effectively treat men with nonbacterial prostatitis-like symptoms.

Figure 8

REDUCTION IN NIH-CPSI SCORES[113]



Adjunctive Therapies

In addition to oral PPS, adjunctive strategies for the management of IC or CP/CPPS include alpha-blockers, analgesics, and/or antihistamines, as well as nonpharmacologic interventions utilized in the management of IC in women (ie, diet modifications and behavioral therapies). Alpha-blockers relax the prostate and bladder smooth muscles, facilitating improvements in urine flow and lower urinary tract symptoms (LUTS). As such, alpha-blocking agents are commonly used to reduce the pain and urinary symptomatology associated with chronic prostatitis syndromes.[114]

Summary

There are numerous similarities in pathophysiologies and clinical presentations of CP/CPPS and IC leading some individuals to suggest that the two entities the same. Diagnosis entails history, physical examination, and an absence of bacteria in urine or prostate-specific specimens. Symptom-specific questionnaires such as the PUF can help determine if the source of the pain is of bladder origin. Although both conditions have a nonbacterial in etiology, they have traditionally been managed – unsuccessfully – with antibiotics. Recently, randomized studies have demonstrated the efficacy and safety of oral PPS in managing CPPS and IC in men as well as women.

CONCLUSIONS

IC is a CPPS of bladder origin, characterized by pelvic pain and urinary frequency and urgency in the absence of other defined bladder pathology. The pain can range from mild discomfort to debilitating pain. Ramifications to QOL can be substantial — IC can significantly impair the ability to work full-time and causes dyspareunia in 60% of patients. Patients with IC score lower on QOL detectors than patients undergoing dialysis or with other chronic illnesses including diabetes and asthma.

IC is believed to affect as many as 1 in 4.5 women, indicating that it is far more common that previously believed. However, gynecologists rarely consider the bladder to be the source of pelvic pain, and therefore frequently misdiagnose IC as endometriosis, recurrent UTIs, and/or pelvic adhesions. Confounding the diagnosis of IC is the high rate of comorbidity between IC and other causes of CPP, as well as the absence of any definitive diagnostic test. Nevertheless, the introduction of the PUF questionnaire can help clinicians easily and readily identify patients who have a bladder component of their pelvic pain. Any patient who scores 5 or higher on the PUF scale is likely to have IC. The PST can be reserved for those patients with symptoms of IC and low PUF scores. Classic, ulcerative IC is rare, and fewer than 10% of patients with IC will demonstrate Hunner's ulcers upon cystoscopy. Consequently, cystoscopy with or without hydrodistention is uncommonly used solely for diagnostic purposes unless the patient has concomitant risk factors for bladder cancer and/or microscopic or gross hematuria.

Until the introduction of oral PPS, the only FDA-approved treatment for IC was intravesical instillations with DMSO, which was associated with at least initial moderate success. In comparison with DMSO, PPS repairs the defective GAG layer underlying IC, providing patients with gradual symptomatic relief and long-term remissions. Patients with long-standing and/or severe disease often require combination therapy utilizing oral PPS as the foundation. Adjunctive pharmacologic therapies include analgesics, antispasmodics, anticholinergics, amitriptyline, and/or antihistamines and antidepressants; nonpharmacologic interventions, such as diet modification and behavioral therapy, can be used to supplement the pharmacologic management. An anesthetic intravesical solution that combines PPS or heparin with sodium bicarbonate and lidocaine may be indicated for patients who require immediate, albeit temporary, relief of the pain and urgency symptoms associated with IC.

The clinical presentation of IC in men is nearly identical to the presentation of Category III prostatitis, CP/CPPS. In fact, it is believed that many men who are diagnosed with CP/CPPS have IC. CP is a common condition, affecting approximately 9% of men in the United States; the overwhelming majority of these men (90% to 95%) have nonbacterial prostatitis (CP/CPPS). When combined with history, pelvic examination, and normal/negative laboratory results, the PUF can identify men who have a bladder component — such as IC — of their pelvic pain/CP. Recent studies have demonstrated the safety and efficacy of oral PPS in the management of IC and CP/CPPS in men as well as women when used as either monotherapy or in conjunction with other pharmacologic and/or nonpharmacologic therapies.

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CHRONIC PELVIC PAIN OF BLADDER ORIGIN: A FOCUS ON INTERSTITIAL CYSTITIS

Instructions:
This activity should take approximately 2 hours to complete. The participant should, in order, read the educational objectives contained in this monograph, answer the 10-question multiple-choice post-test on page 22, and complete the registration/evaluation form. If you wish to receive CME credit and a certificate, please mail/fax a copy of your completed answers to:

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POST-TEST/SELF ASSESSMENT

Please record your answers on the answer form in the space provided.

1. Which of the following symptoms of chronic pelvic pain syndromes overlap with those specific to interstitial cystitis?
   a. Nocturia
   b. Urinary urgency and frequency
   c. Painful intercourse
   d. All of the above
   e. None of the above

2. Which vulvodynia syndrome may be related to interstitial cystitis?
   a. Cyclic candidiasis
   b. Vulvar vestibulitis syndrome
   c. Vestibular papillomatosis
   d. Vulvar dermatoses
   e. Cytolytic vaginosis

3. Historically, a diagnosis of interstitial cystitis required the presence of:
   a. Severe nocturia (>12 times/night)
   b. Hunner's patch
   c. Urinary stress incontinence
   d. All of the above
   e. None of the above

4. It is now estimated that what proportion of women have IC?
   a. 1 in 52
   b. 1 in 25
   c. 1 in 17
   d. 1 in 4.5

5. The most prevalent hypothesis underlying the pathophysiology of IC concerns:
   a. Autoimmunity
   b. The presence of unusual organisms in bladder cells not yet detectable
   c. An alteration of the GAG layer
   d. Hypersensitization of sensory nerve fibers triggering neurogenic inflammation

6. IC should be suspected in patients with:
   a. Recurrent UTIs
   b. OAB that does not respond to anticholinergic agents
   c. Dyspareunia and/or pain surrounding intercourse
   d. History – or suspicion – of endometriosis
   e. All of the above
   f. None of the above

7. Which of the following diagnostic findings is most suggestive of IC?
   a. Petechial hemorrhages upon cystoscopy and hydrodistention
   b. A PUF score ≥10 points
   c. History of cyclic or noncyclic pelvic pain with urinary urgency/frequency
   d. A negative RS

8. Oral PPS is believed to act by:
   a. Reducing bladder capacity
   b. Replenishing a defective GAG layer and inhibiting inflammatory processes
   c. Neutralizing acidity in the bladder
   d. Exerting muscle-relaxing properties and inhibiting mast cell secretion

9. Which of the following adjuvant therapies may also exacerbate symptoms of IC?
   a. Amitriptyline
   b. Anticholinergics
   c. NSAIDs
   d. Antihistamines

10. In men, interstitial cystitis is most commonly misdiagnosed as:
    a. Acute bacterial prostatitis
    b. Benign prostatitic hyperplasia
    c. Chronic prostatitis/chronic pelvic pain syndrome
    d. Urinary tract infection

CME REGISTRATION/POST-TEST ANSWER FORM/EVALUATION

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6. ___ 7. ___ 8. ___ 9. ___ 10. ___

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Figure 2

PELVIC PAIN AND URGENCY/FREQUENCY PATIENT SYMPTOM SCALE

Patient's Name:_____ Today's date: _____

Please circle the answer that best describes how you feel for each question.

		0	1	2	3	4	SYMPTOM SCORE	BOTHER SCORE
1	How many times do you go to the bathroom during the day?	3-6	7-10	11-14	15-19	20+		
2	a. How many times do you go to the bathroom at night?	0	1	2	3	4+		
	b. If you get up at night to go to the bathroom, does it bother you?	Never bothers	Occasionally	Usually	Always			
3	Are you currently sexually active? YES _____ NO _____							
4	a. **IF YOU ARE SEXUALLY ACTIVE,** do you now or have you ever had pain or symptoms during or after sexual activity?	Never	Occasionally	Usually	Always			
	b. If you have pain, does it make you avoid sexual activity?	Never	Occasionally	Usually	Always			
5	Do you have pain associated with your bladder or in your pelvis (vagina, labia, lower abdomen, urethra, perineum, penis, testes, or scrotum)?	Never	Occasionally	Usually	Always			
6	a. If you have pain, is it usually		Mild	Moderate	Severe			
	b. Does your pain bother you?	Never	Occasionally	Usually	Always			
7	Do you still have urgency after you go to the bathroom?	Never	Occasionally	Usually	Always			
8	a. If you have urgency, is it usually		Mild	Moderate	Severe			
	b. Does your urgency bother you?	Never	Occasionally	Usually	Always			

SYMPTOM SCORE (1, 2a, 4a, 5, 6a, 7, 8a)	
BOTHER SCORE (2b, 4b, 6b, 8b)	
TOTAL SCORE (Symptom Score + Bother Score) =	

Total score ranges are from 1 to 35.
A total score of 10-14 = 74% likelihood of positive PST; 15-19 = 76%; 20+ = 91% Potassium Positive

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